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Editorial Open Access

Antituberculosis Agents on the Horizon

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Editorial

Tuberculosis (TB) remains a global health problem despite the availability of efficacious drug therapies and efforts being made to decrease its incidence. TB is the second leading cause of death globally due to an infectious disease behind the human immunodeficiency virus (HIV) [1]. TB is caused by the infective bacillus organism *Mycobacterium tuberculosis* which primarily affects the lungs. There are two forms of TB: latent TB infection (LTBI) and active TB disease. In LTBI the organisms are non-replicating and the infected individual does not display symptoms of the infection. Active TB disease is seen when the organism slowly replicates inside the host cells. Patients exhibit signs and symptoms of the infection during active TB [2].

Current FDA approved drugs considered central first-line treatment agents against *M. tuberculosis* are isoniazid (INH), rifampim (RIF), ethambutol (EMB), and pyrazinamide (PZA). Although treatment regimens for TB exist, an increase in adherence failure rates is occurring as a result of the lengthy duration of multidrug therapy [2,3]. Furthermore, poor adherence combined with the resilient ability of *M. tuberculosis* to acclimate to environmental changes and its slow rate of growth has led to a rise in drug resistance [4-6]. The emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) strains of TB has complicated the capability of known medications to treat TB. MDR TB occurs when *M. tuberculosis* strains are at least resistant to RIF and INH. XDR-TB is also defined as MDR TB and is resistant to any fluoroquinolone and at least one of the second-line injectable agents (amikacin, kanamycin and/or capreomycin) [7]. Therefore, there are ongoing efforts to develop new agents with different mechanisms of actions and/or structures as potential TB drugs. Three areas of interests for new treatment options are adjunct verapamil, spectinamides, and pentacyclic nitro furans. An overview of each potential treatment is discussed below.

M. tuberculosis is able to grow intracellularly in the host cell and prompt macrophage-induced drug tolerance to agents with antituberculosis activity. These actions are facilitated through drug efflux pumps, specifically efflux pump Rv1258c when discussing RIF [8]. Efflux pumps expel drugs and noxious agents from the cell leading to drug resistance and intracellular growth respectively [9]. Verapamil, verapamil's R-isomer, and norverapamil (a metabolite of verapamil) help inhibit this macrophage-induced drug tolerance to RIF, rifabutin, and INH. It was concluded that verapamil's calcium channel blocking mechanism did not play an active role compared to its ability to inhibit bacterial efflux pumps. This conclusion was derived after R-verapamil and norverapamil, both having very limited cardiac activity compared to verapamil, were found to have similar efficacies at inhibiting macrophage-induced tolerance.Verapamil's continued blockade of RIF tolerance after administration with supplemental $CaCl_2$ also supports this finding. However, once resistance has occurred the addition of an efflux pump inhibitor does not restore susceptibility of the resistant drug. This was seen when a strain of RIF-resistant TB displayed no further intracellular killing following the addition of verapamil. The discovery of drug tolerance inhibition with efflux-pump blockers suggests that verapamil could potentially be used as an adjunct agent to some treatment regimens to shorten the course of drug therapy by up to two months as seen in murine models [8,10].

Spectinamides are a new class of semi-synthetic spectinomycin analogs being evaluated for the treatment of tuberculosis. In vivo these compounds display strong potency through their selective activity against the ribosome and ability to avoid pump-mediated efflux by structural modification [11]. This potent anti-tubercular action spans over prototypes of acute and chronic infections, MDR-strains, and XDR-types of tuberculosis. As with spectinomycin these agents exhibit a post-antibiotic effect (PAE) which can be enhanced if the analog is chlorinated. Spectinamide's pharmacodynamic property of time-dependent killing is opposite of that demonstrated by aminoglycosides. The structural differences from spectinomycin allow the spectinamides to have narrow-spectrum anti-tubercular activity leading to a lesser potential for adverse reactions. The targeted effect results in a cytotoxic free action with no effect on the cardiac hERG potassium ion channel and a lack of CYP450 enzyme inhibition. Cross resistance to TB treatments that inhibit protein synthesis is not observed with these compounds. The compilation of this data suggests the potential use of spectinamides as clinical anti-tubercular agents [11].

A pentacyclic hybrid nitrofuran compound resulting from integration of the cyclic traits of OPC-67683 (delamanid) into a tetracyclic nitrofuranylisoxazoline with promising TB activity has also been reported. Due to its activity against non-replicating bacteria this pentacyclic nitro furan [12] may be a viable target for LTBI treatment options. In vivo this new compound has inadequate oral bioavailability, but displays better metabolic stability with no adverse effects. The MIC of this nitrofuran shows that potency against *M. tuberculosis* is sustained. A drop in the MIC of RIF when the pentacyclic nitro furan [12] is co-administered demonstrates its synergistic effect with existing drug therapies. However, this synergism was not exhibited when the nitrofuran was paired with INH, EMB, streptomycin, or linezolid. Other positive areas for the nitrofuran are its PAE and reduced possibility for cross-resistance to other nitroimidazole drugs used to treat TB. Favorably, the PAE of the nitrofuran was comparable to the long PAE recognized with isoniazid. Reduction of cross resistance was highlighted by continued activity of nitrofuran after removal of the three known activation genes of both nitroimidazoles OPC-67683 and PA-824. While the pentacyclic hybrid nitrofuran compounds suggest viable areas of research against non-replicating *M. tuberculosis* further studies to improve the pharmacodynamics and efficacy of the series are still justified [12].

Until TB persistence is eliminated as a global problem, antituberculosis therapies that effectively enhance selective activity

against *M. tuberculosis*, inhibit drug resistance, and shorten treatment duration are highly desired. Research is being done on newly developed compounds and existing drugs that are thought to possess those characteristics. Although more studies are needed, adjunct verapamil, spetinamides, and pentacyclic nitro furans have created possible avenues for future treatment options.

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